The objection to the specification noted on page 2 of Paper No. 19 (Office Action dated January 2, 2003) is obviated by the above. Withdrawal of the objection is requested.

The Section 112, second paragraph, rejection of claims 17-39 is obviated by the above. Reconsideration and withdrawal of the rejection are requested.

The Section 102 rejection of claims 17-26 and 28-31 over Corral (PNAS (1993) 90:8538-42) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

As discussed with the Examiners during the interview, the applicant believes that Corral et al, describe a method for investigating rearrangement of the MLL gene in acute leukeamia patient samples. In this study the goal is to characterize the breakpoint region of a fusion gene involving the MLL gene and to discover new partners of the MLL gene which may account for unknown fusion partner genes. To this aim Corral et al describe the following two methods:

The first method of Corral is aimed at analyzing the junction between the MLL 5' gene, and the 3' fusion partner gene, of the fusion gene; the partner gene being known. This is achieved in four main steps:

1) Performing a reverse transcription of the total RNA of the sample using a random primer that hybridize non specifically to any RNA sequences present in the sample;
2) Performing a specific PCR on the synthetized cDNA using pair of primers selected to amplify the junction between the MLL gene and the fusion partner

gene (ex AF4 and ENL in the article, page [PLEASE INSERT PAGE]...., section 1);

3) Cloning the resulting product in a vector; and

4) Sequencing the cloned product to define precisely the sequences of nucleotides involved in the junction and hence the break point position in both MLL gene and the known partner gene.

The second one is aimed at identifying new unknown fusion partner genes, if any, and then describing the junction between the 5' MLL gene, and the 3' fusion partner gene, of the identified fusion gene. This second method involves the following six main steps.

1) Performing a "Southern Blot" on the DNA of the patient sample (*described as a Filter Hybridisation in Material and methods: DNA analysis of acute leukemia samples: Filter Hybridization, page 8538)* to confirm the presence of a MLL rearrangement and characterize roughly the breakpoint position on the 5' MLL gene by using two exon specific labeled probes;

2) Performing a reverse transcription of the total RNA of the sample using a random primer that hybridizes non specifically to any RNA sequences present in the sample and bearing an anchor that displays a unique sequence not found in any sequences present in the sample;

3) Performing a specific PCR on the synthetized cDNA using pairs of primers selected to:

a) amplify the MLL gene and any downstream sequences by means of an anchor specific primer; and

b) providing a reasonable fragment length for subsequent cloning and sequencing (this latter selection is based on the information of the step 1 (Filter hybridization));

5) Cloning the resulting product in a vector; and

6) Sequencing the cloned product to identify the 3' fusion partner gene in and define precisely the sequences of nucleotides involved in the junction and hence the breakpoint position in both MLL gene and the unknown partner gene.

The present patent application describes and claims methods and products useful in detecting a fusion gene and identifying the fusion partner fused to a target gene (i.e., MLL) among known fusion partner gene candidates (i.e. AF4, 9, 10 etc). To this end, the inventors describe a method achieved in the following four main steps:

1) Performing a reverse transcription of the total RNA of the sample using a random primer that hybridizes non specifically to any RNA sequences present in the sample and bearing an anchor that displays a unique sequence not found in any sequences present in the sample;

2) Performing PCR, preferably long distance PCR, on the synthesized cDNA using a unique pair of primers selected to amplify indiscriminately the target (i.e., MLL) gene and any downstream sequences by means of an anchor specific primer;

3) Performing a specific hybridization of the resultant PCR product to known fusion partner gene specific sequence probes; and

4) Detecting the presence of specific hybridization to given sequence probes reactions by the means of, for example, a reporter system.

As discussed with the Examiners during the interview of January 29, 2003, there are at least the following two main differences between the teachings of Corral and the presently claimed invention:

1) Corral teaches cloning and sequencing reactions to identify new fusion partners and define the junction whereas the presently claimed invention requires hybridization of PCR products with probes specific for the fusion partner; and

2) The presently claimed invention provides for the use of a pair of primers which indiscriminately amplify any cDNA of the fusion gene that is then used for subsequent steps, irrespective of their size, while Corral requires a selection of the pair of primers based on a previous Filter hybridisation of the analyzed sample to limit the size of the resulting PCR product.

These differences emphasize that Corral teaches how to discover new fusion partner genes and not how to screen, in any practically manner, for the presence of known fusion partner gene in a clinical sample, as may be performed with the presently claimed method and products.

As Corral fails to teach each and every aspect of the presently claimed invention, the Section 102 rejection of claims 17-26 and 28-31 over Corral should be withdrawn.

The Section 102 rejection of claims 32-36 over Cerelli (U.S. Patent No. 5,620,861) is traversed. Reconsideration and withdrawal of the rejection are requested as Cerelli fails to teach each and every aspect of the claimed invention. In the event any rejection of the claims is maintained over Cerelli, the Examiner is requested to indicate, with particularity, where the claimed elements of the present invention are found in Cerelli.

The Section 102 rejection of claims 32-35 and 37-38 over Chee (U.S. Patent No. 5,837,832) is traversed. The rejection should be withdrawn as Chee's general teachings of microarrayed hybridization probes fail to place in the hands of the public the presently claimed invention. In the event any rejection based on Chee is maintained, the Examiner is requested to explain, with specificity, where the presently claimed invention may be found in the cited document.

The Section 103 rejection of claim 27 over Corral and Hoeltke (Cellular and Molecular Biology (1995) 41(7):883-905) is traversed and should be withdrawn as Hoeltke fails to cure the deficiencies of Corral noted above. The presently claimed invention is submitted to be patentable over the cited art.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

29. (Twice Amended) The method of claim 39, wherein said cancer [pathology] is leukemia.

30. (Twice Amended) The method of claim 39, wherein said cancer is a [pathology concerns] solid tumor[s].

31. (Amended) The method of claim 30, wherein said [pathology concerns] cancer is a Ewing tumor[s].

32. (Twice Amended) A kit for identifying DNA sequences of fusion genes, said fusion genes comprising a target gene and a fusion partner, said kit comprising: one pair of primers wherein one of the primers of the pair is complementary to the nucleotide sequence of the target gene and binds to said target gene to form a complex which provides indiscriminate amplification, in the presence of Taq polymerase, and the other primer is an anchored primer; and at least one proble specific for said fusion partner, said at least one probe being bound to a solid support[A kit for the detection and identification method according to claim 39, comprising primers specific for the target genes and reagents for carrying out the anchored PCR and detection step].

33. (Amended) A kit according to claim 32, further comprising [agents] at least one agent capable of cleaving or blocking the gene of the polypeptidic nucleic acids or of the ribozymes.

36. (Amended) A kit according to claim 32[35], wherein said at least one probe[s have] is bound to the solid support through a biotin group [on their 5' end and are] bonded to streptavidine coupled to said support [plates].

37. (Amended) A kit according to claim 32[34], wherein the [probes are bonded to] solid support is a miniaturized support.

38. (Amended) A kit according to claim [37]32 wherein the [miniaturized] support is a DNA chip.

39. (Twice Amended) An *in vitro* diagnostic method for detecting and identifying DNA sequences of fusion genes comprising a target gene and a fusion partner, said fusion genes being involved in cancer [pathologies] associated with rearrangements of [a] the target gene, wherein a patient DNA or cDNA is subjected to an anchored PCR[, *in vitro*,] comprising:

a[.]) indiscriminately amplifying all of the DNA or cDNA of said fusion genes [one or more] PCR, with one pair of primers, one of the primers being complementary to the nucleotide sequence of the target gene, the other primer being an [complementary]

anchored primer, wherein all the DNA or cDNA sequences [adjacent to] of the target gene are amplified,

b[.]) obtaining PCR products,

c[.]) hybridizing the PCR products with probes specific for said fusion partner, [either the target gene or any adjacent DNA sequences],

d[.]) detecting [the presence of] rearrangements of the target gene, and[, if any rearrangement is detected,] identifying the fusion genes of any detected rearrangements [DNA sequences involved].

Figure 1A

Reverse transcription

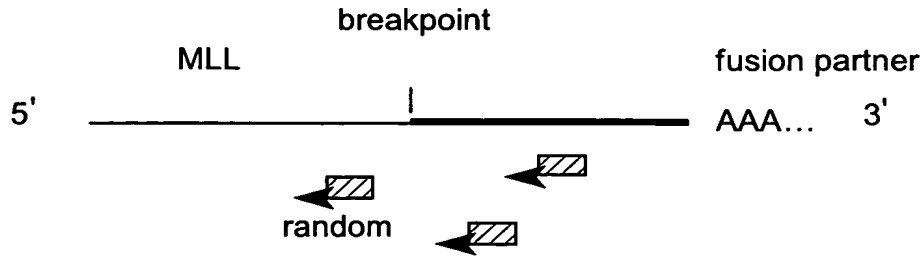

Figure 1B

Long distance PCR

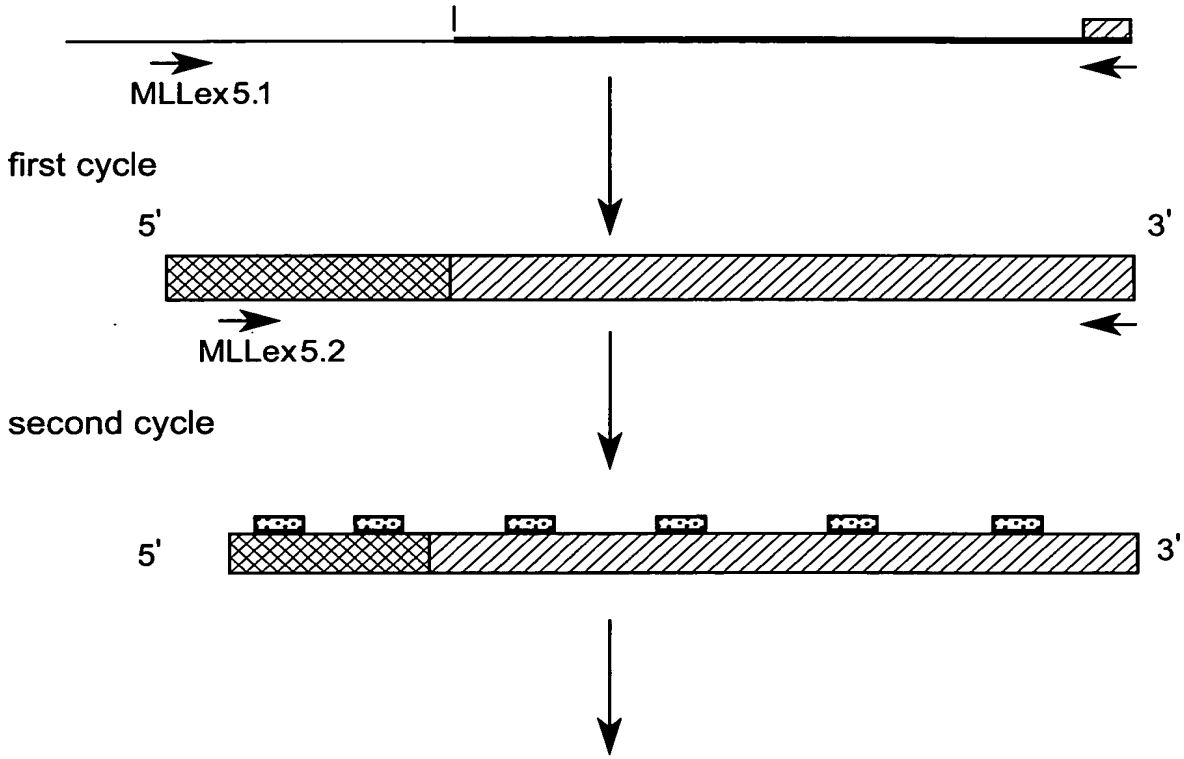

Figure 1c

ELISA detection